PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.10.2004

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
P32498PC01	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK 03/00483	09.07.2003	11.07.2002

Applicant
UPFRONT CHROMATOGRAPHY A/S et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ipinazar, P Tel. +49 89 2399-8131

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

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Plougmann & Vingtoft

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P32498PC01	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00483	International filing date *(day/month/year)* 09.07.2003	Priority date *(day/month/year)* 11.07.2002
International Patent Classification (IPC) or both national classification and IPC B01D15/00		
Applicant UPFRONT CHROMATOGRAPHY A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.02.2004	18.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Nissen, V Telephone No. +49 89 2399-8619

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00483

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-42 as originally filed

Claims, Numbers

1-26 as amended (together with any statement) under Art. 19 PCT

Drawings, Sheets

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 13-17, 19-24

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. see seperate sheet are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. see seperate sheet

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

bacteria or any harmful substance therefrom has/have also not been searched.

1.5 Accordingly subject matter pertaining to such embodiments cannot be subject to the present international preliminary examination (R. 66.1(e) PCT).

1.6 Nevertheless, as said embodiment is claimed in the alternative in claim 2 to a searched embodiment all methods claims 1-12 can (at least in part) be examined based on the search report.

2. The ISA also raised objections in respect of original claims 13 and 14 for relating to methods of treatment of the human or animal body (R. 39.1(iv) PCT).

2.1 With the demand the applicant has altered the category of claims 13 and 14 with dependent claims to a use of an adsorption medium for preparing an adsorption column (suitable) for continuous therapeutic treatment. Furthermore, the new claims 13 and 14 now specify that said treatment involves flowing blood through the column at such a rate that a fluidised bed is formed.

2.2 The latter feature is apparently introduced to establish unity with the above mentioned first searched embodiment. However, as claims 13 and 14 pertain to a use of an adsorption medium for preparing a column and not to the use of the column, any feature relating to the desired subsequent use of the column is essentially not limiting on the claimed subject matter.

2.3 Accordingly, and except as indicated above and below, these claims do not form a common both novel and inventive concept with the first embodiment (R. 13 PCT) for the reasons pointed out in the invitation to pay further fees according to PCT Art. 17(3) and R. 40.1. Consequently the claims are only searched in part for which reason no complete examination can be carried out (R. 66.1(e) PCT).

3. Moreover, claims 13 and 14 have been amended by removing the reference to the adsorption medium being in the form of particles.

3.1 No basis for said amendment has been cited, and as it has been consistently stated throughout the description that the medium according to the invention is in the form of particles, the amendment appears to violate Art. 34(2)(b) PCT. Reference is made to R. 70.2(c) PCT. By inherence this objection also apply to claims 15-17 and 19-24. Dependent claims 18 and 25+26 refer to "the particles",

albeit without anteceding basis (Art. 6 PCT).

4. It should be noted that although the claims which originally defined methods of treatment of the human or animal body, i.e. claims 13 and 14 (with dependent claims) have been amended to overcome said objection, it is found that the methods of claims 1 and 2 seem to define such treatment implicitly (R. 39.1(iv) PCT).

4.1 In fact, the new wording of claims 13 and 14 using verbs in presence and the maintenance of claim 16 still makes it unclear whether the applicant intends to include the step of obtaining and delivering the blood to/from the patient in the claimed use (Art. 6 and R. 39.1(iv) PCT).

4.2 The present examination has been carried out under the assumption that the methods (and uses) in question are operated isolated from any animal or human being in vitro/ex vivo.

5. It appears to be abundantly known to treat blood by adsorption where the adsorbent has an affinity towards various toxins i.a. the LPS-portion of Gram-negative bacteria.

5.1 The applicant cites himself i.a. Jaber & Pereira [vide page 5], Shoji et al. [page 7] and others which have experimented using immobilised Polymyxin B compounds as adsorbent.

5.2 It is presently not clear how the present invention as claimed differ from said prior art (R. 5.1(a)(iii) and Art. 33(2) PCT).

6. D1 discloses a method of removing LPS from Gram-negative bacteria from blood in an extracorporeal circulation treatment [column 3, lines 13-25]. A molecule having affinity for the LPS is covalently bound to plastic beads (particles).

6.1 D1 is silent in respect of the placement of the particles in an adsorption column in an amount of 80 vol.% or less, and D1 does not suggest to drive the column as a fluidised bed.

6.2 Accordingly all claims appear to be novel over D1.

6.3 D5 presents a similar teaching, namely that an antimicrobial agent capable of binding LPS can be immobilised on a bead for use in a column for treating blood [page 2, lines 41-44; page 7, lines 14-19; page 10, line 50-page 11, line 52; in particular paragraphs 92 and 93]. D5 is likewise silent in respect of the placement of the particles in an adsorption column in an amount of 80 vol.% or less, and in respect of driving the column as a fluidised bed.

6.4 For the sake of completeness it is noticed that D4 also suggests to remove toxins from blood using an adsorption column in an extracorporeal circulation treatment [page 1, lines 5-12; page 6, lines 5-8], but does not explicitly mention LPS. Nevertheless, the removal of toxins associated with Gram-positive bacteria are mentioned.

6.5 Starting from any of the above prior art [vide item 5-6.4], and considering the technical effect the differing essential feature(s), i.e. of using a fluidised bed (and thus necessarily of having a sedimented packing percentage well below 100%, i.e. of 80%), this appears merely to be to prevent clogging of the column due to larger molecules etc. [vide present application page 9, lines 12-23].

6.6 Nevertheless, the various advantages of using fluidised or expanded beds are well known in the art of unit operations [vide for instance D2 and D3].

6.7 It is, furthermore, considered to be well within the capabilities of the person skilled in the art to determine the optimum conditions in terms of flow rate, bead size and density etc.

6.8 As no particular unexpected effects can be seen to be the consequence of the features as defined in any of the present claims, these are found to lack and inventive step (Art. 33(3) PCT).

7. The subject matter of several claims is unclear, confusing or redundant (Art. 6 PCT):

7.1 For instance embodiment i) of claim 2 appears essential identical to the embodiment of claim 1 (lack of conciseness: Art. 6 and R. 6 PCT).

7.2 It is unclear how it is to be determined from the method (operated isolated from any animal or human being in vitro/ex vivo) according to claim 3 whether the blood

is "capable of being reinfused" into a mammal. In principle any liquid is capable albeit not necessarily suitable for infusion.

7.3 Claim 4 is redundant.

7.4 As mentioned in item 2.2 above essentially only those features actually involved with the use for preparation of the column in claims 13-26 are found limiting to the claimed subject matter. Consequently all other features in particular those listed in respect of the intended subsequent use of the column are redundant to the extent they do not imply further properties of the column itself. In particular claims 16 and 17 are unclear and redundant.

7.5 Claim 16 is furthermore unclear as it refers to claim 13 where no steps a), b) and c) are defined (Art. 6 PCT).

8. In the present case the two part form of claiming seems appropriate (R. 6.3(b) PCT).

9. Industrial applicability is self-evident for the subject matter of all claims (Art. 33(4) PCT).

Reference is made to the following documents:

D1: US-A-6 090 292 (OTTO VEIT ET AL) 18 July 2000 (2000-07-18)
D2: JAN FEUSER ET AL: "Cell/adsorbent interactions in expanded bed adsorption of proteins" BIOSEPARATION, vol. 8, 1999, pages 99-109, XP002259859
D3: US-A-5 837 826 (ROBICHAUD MICHAEL J ET AL) 17 November 1998 (1998-11-17)
D4: EP-A-1 057 529 (TORAY INDUSTRIES) 6 December 2000 (2000-12-06)
D5: EP-A-0 955 312 (SEIKAGAKU KOGYO CO LTD) 10 November 1999 (1999-11-10)
D6: WO 02/053251 A (LIHMES APS ;LIHME ALLAN OTTO FOG (DK)) 11 July 2002 (2002-07-11)

1. The International Search Authority (ISA) found the present application to lack unity. Reference is made to the invitation to pay further fees according to PCT Art. 17(3) and R. 40.1.

1.1 The originally claimed embodiments were essentially according to claim 1 where the LPS-portion of Gram-negative bacteria present in blood is adsorbed in a fluidised bed, and according to claim 2 where the LPS-portion of Gram-negative bacteria or Gram-positive bacteria or any harmful substance therefrom present in blood is adsorbed in any suitable bed.

1.2 No further search fees were paid and only the subject matter of original claims 1, 3-15 and 17-26 was apparently searched insofar they relate to the claim 1 embodiment.

1.3 With the Demand the applicant submitted amended claims under Art. 19 PCT. It appears that it is intended to introduce a common feature between the searched embodiment and the unsearched embodiment, namely in terms of the use of a fluidised bed.

1.4 Nevertheless, it is noticed that as original claim 2 etc. has not been searched, the alternative embodiment(s) of said claim pertaining to the removal of Gram-positive

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. see separate sheet .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-12, 18, 25-26*
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12, 18, 25-26
Industrial applicability (IA)	Yes:	Claims	1-12, 18, 25-26
	No:	Claims	

2. Citations and explanations

see separate sheet

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25 AUG. 2004

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